

**Clinical trial results:****A Phase III Double-blind, Randomized, Placebo-Controlled Study assessing the Efficacy, Safety and Tolerability of Idebenone in Patients with Duchenne Muscular Dystrophy Receiving Glucocorticoid Steroids
Summary**

EudraCT number	2016-000602-10
Trial protocol	DE BE NL SE GB ES AT FR IT IE HU BG
Global end of trial date	01 December 2020

Results information

Result version number	v2 (current)
This version publication date	08 January 2023
First version publication date	26 June 2022
Version creation reason	• New data added to full data set new updated study data available
Summary attachment (see zip file)	company statement (2022-06-10_Statement_EudraCT_signed.pdf)

Trial information**Trial identification**

Sponsor protocol code	SNT-III-012
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02814019
WHO universal trial number (UTN)	-
Other trial identifiers	US IND: 103801

Notes:

Sponsors

Sponsor organisation name	Santhera Pharmaceuticals (Switzerland) Limited
Sponsor organisation address	Hohenrainstrasse 24, Pratteln, Switzerland, 4133
Public contact	Julien Gaudias, Santhera Pharmaceuticals (Switzerland) Limited, +41 79 811 01 98, julien.gaudias@santhera.com
Scientific contact	Julien Gaudias, Santhera Pharmaceuticals (Switzerland) Limited, +41 79 811 01 98, julien.gaudias@santhera.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2020
Global end of trial reached?	Yes
Global end of trial date	01 December 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of idebenone compared to placebo, in delaying the loss of respiratory function in patients with DMD receiving glucocorticoid steroids as measured by changes in Forced Vital Capacity percent predicted (FVC %p) using clinic-based spirometry

Protection of trial subjects:

This study was conducted according to the guidelines of Good Clinical Practice (GCP), ICH E3 (CPMP/ICH/135/95), the US Code of Federal Regulations governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), in compliance with the World Medical Assembly Declaration of Helsinki and its most recent amendments and applicable local regulatory requirements and law.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 36
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 55
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	United States: 72
Worldwide total number of subjects	264
EEA total number of subjects	145

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	28
Adolescents (12-17 years)	154
Adults (18-64 years)	82
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 395 patients were screened and 267 were enrolled in the study (132 patients each in the idebenone and placebo arms)

Period 1

Period 1 title	Baseline to Week 78 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	idebenone

Arm description:

Idebenone arm: 900 mg idebenone per day (two 150 mg tablets to be taken orally, three times a day with meals).

Arm type	Experimental
Investigational medicinal product name	idebenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

900 mg idebenone per day (two 150 mg tablets to be taken orally, three times a day with meals).

Arm title	Placebo
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Arm description:

Matching Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

two tablets to be taken orally, three times a day with meals.

Number of subjects in period 1	idebenone	Placebo
Started	132	132
Completed	99	89
Not completed	33	43
Consent withdrawn by subject	8	12
FAILURE TO MEET CONTINUATION CRITERIA	1	-
Adverse event, non-fatal	4	3
Death	3	1
xxxxxxxxxxxxxxxxxxxx	16	-
PROTOCOL-SPECIFIED WITHDRAWAL CRITERION MET	-	2
Lost to follow-up	-	3
xxxxxxx	-	21
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	idebenone
Reporting group description:	
Idebenone arm: 900 mg idebenone per day (two 150 mg tablets to be taken orally, three times a day with meals).	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo	

Reporting group values	idebenone	Placebo	Total
Number of subjects	132	132	264
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	13	15	28
Adolescents (12-17 years)	78	76	154
Adults (18-64 years)	41	41	82
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	132	132	264

End points

End points reporting groups

Reporting group title	idebenone
Reporting group description: Idebenone arm: 900 mg idebenone per day (two 150 mg tablets to be taken orally, three times a day with meals).	
Reporting group title	Placebo
Reporting group description: Matching Placebo	

Primary: Change From Baseline in Forced Vital Capacity Percent Predicted (FVC %p) at Week 78

End point title	Change From Baseline in Forced Vital Capacity Percent Predicted (FVC %p) at Week 78
End point description: Delaying the loss of respiratory function in patients with Duchenne muscular dystrophy (DMD) receiving glucocorticoid steroids as measured by changes in FVC%p (Percent Predicted Forced Vital Capacity) from Baseline to Week 78 using hospital based spirometry	
End point type	Primary
End point timeframe: Baseline to Week 78	

End point values	idebenone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: FVC %p				
least squares mean (standard deviation)				
Change From Baseline in Forced Vital Capacity Perc	-9.93 (± 7.446)	-8.39 (± 6.218)		

Statistical analyses

Statistical analysis title	Analysis of FVC%p
Statistical analysis description: Slope analysis assuming MNAR Estimated treatment difference of slopes (as annual rate of change in FVC%p)	
Comparison groups	idebenone v Placebo

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.9403
Method	Random Coefficient Regression Model
Parameter estimate	Median difference (net)
Point estimate	0.05
Confidence interval	
level	Other: 99.46 %
sides	2-sided
lower limit	-1.83
upper limit	1.93
Variability estimate	Standard error of the mean
Dispersion value	0.68

Notes:

[1] - Estimated treatment difference of slopes (as annual rate of change in FVC%p over 78 Weeks)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Informed consent signature date to end of study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	Idebenone
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Idebenone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 132 (12.88%)	14 / 132 (10.61%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	3	1	
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	3 / 132 (2.27%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fat embolism			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thoracic vertebral fracture subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial fibrosis subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systolic dysfunction subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiogenic shock			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Surgical and medical procedures			
Orthopaedic procedure			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenotomy			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Benign intracranial hypertension			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung consolidation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteomyelitis chronic			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Idebenone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 132 (91.67%)	120 / 132 (90.91%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	2	1	
Peripheral venous disease			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lymphoedema			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Ankle operation			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Mole excision			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Orthopaedic procedure			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Tenotomy			
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)	
occurrences (all)	1	2	
Ear tube insertion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Pyrexia		
subjects affected / exposed	11 / 132 (8.33%)	13 / 132 (9.85%)
occurrences (all)	14	18
Influenza like illness		
subjects affected / exposed	4 / 132 (3.03%)	3 / 132 (2.27%)
occurrences (all)	5	3
Fatigue		
subjects affected / exposed	3 / 132 (2.27%)	1 / 132 (0.76%)
occurrences (all)	3	1
Malaise		
subjects affected / exposed	3 / 132 (2.27%)	1 / 132 (0.76%)
occurrences (all)	3	1
Peripheral swelling		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	2	1
Chest pain		
subjects affected / exposed	1 / 132 (0.76%)	3 / 132 (2.27%)
occurrences (all)	1	3
Oedema peripheral		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Pain		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Vaccination site pain		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Vessel puncture site bruise		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Cyst		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Discomfort		
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)
occurrences (all)	0	3

Hyperpyrexia subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	1 / 132 (0.76%) 1	
Injection site pain subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	1 / 132 (0.76%) 1	
Medical device pain subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	1 / 132 (0.76%) 1	
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	1 / 132 (0.76%) 1	
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	1 / 132 (0.76%) 1	
Social circumstances Walking disability subjects affected / exposed occurrences (all)	2 / 132 (1.52%) 2	0 / 132 (0.00%) 0	
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	0 / 132 (0.00%) 0	
Testicular retraction subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	0 / 132 (0.00%) 0	
Genital rash subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	2 / 132 (1.52%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	20 / 132 (15.15%) 33	16 / 132 (12.12%) 20	
Oropharyngeal pain			

subjects affected / exposed	10 / 132 (7.58%)	18 / 132 (13.64%)
occurrences (all)	13	23
Rhinorrhoea		
subjects affected / exposed	6 / 132 (4.55%)	3 / 132 (2.27%)
occurrences (all)	6	4
Acute respiratory failure		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	2	1
Nasal congestion		
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)
occurrences (all)	2	2
Productive cough		
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)
occurrences (all)	2	2
Sleep apnoea syndrome		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	2	1
Asthma		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Epistaxis		
subjects affected / exposed	1 / 132 (0.76%)	8 / 132 (6.06%)
occurrences (all)	1	16
Pulmonary congestion		
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)
occurrences (all)	1	2
Respiratory distress		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Respiratory muscle weakness		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Tachypnoea		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Throat irritation		

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Chronic throat clearing			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Increased upper airway secretion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lung consolidation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pulmonary embolism			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Respiratory depth decreased			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Respiratory failure			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Rhinitis allergic			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Sinus congestion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	6 / 132 (4.55%)	0 / 132 (0.00%)	
occurrences (all)	7	0	
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Mood altered			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Initial insomnia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Panic attack			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Investigations			
Bone density decreased			
subjects affected / exposed	3 / 132 (2.27%)	0 / 132 (0.00%)	
occurrences (all)	3	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 132 (1.52%)	3 / 132 (2.27%)	
occurrences (all)	2	3	
Blood bilirubin increased			

subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	3	0
Blood creatine phosphokinase increased		
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)
occurrences (all)	2	2
Blood glucose increased		
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)
occurrences (all)	2	2
Blood triglycerides		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	2	1
Vitamin D decreased		
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	2	0
Weight increased		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	2	1
Blood chloride decreased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Blood cholesterol increased		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Blood uric acid increased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Blood urine		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Cardiac function test abnormal		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Cardiac imaging procedure abnormal		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0

Crystal urine present		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Ejection fraction decreased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Fibrin D dimer increased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Glomerular filtration rate increased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Heart rate increased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Heart rate irregular		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Lymphocyte count decreased		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Neutrophil count increased		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Oxygen saturation decreased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Platelet count increased		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
QRS axis abnormal		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Red blood cells urine		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1

Urine analysis abnormal		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Weight decreased		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Aspartate aminotransferase increased		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Blood creatinine increased		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Blood potassium decreased		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Blood potassium increased		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Blood urine present		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Breath sounds abnormal		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Crystal urine		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Gamma-glutamyltransferase increased		
subjects affected / exposed	0 / 132 (0.00%)	3 / 132 (2.27%)
occurrences (all)	0	3
Glucose urine present		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Haemoglobin urine		

subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Haemoglobin urine present			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Thyroid hormones increased			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Troponin T increased			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 132 (3.03%)	4 / 132 (3.03%)	
occurrences (all)	6	4	
Femur fracture			
subjects affected / exposed	4 / 132 (3.03%)	2 / 132 (1.52%)	
occurrences (all)	4	2	
Fall			
subjects affected / exposed	3 / 132 (2.27%)	4 / 132 (3.03%)	
occurrences (all)	3	4	
Injury			
subjects affected / exposed	3 / 132 (2.27%)	2 / 132 (1.52%)	
occurrences (all)	4	2	
Joint injury			
subjects affected / exposed	3 / 132 (2.27%)	2 / 132 (1.52%)	
occurrences (all)	3	2	
Muscle strain			
subjects affected / exposed	3 / 132 (2.27%)	1 / 132 (0.76%)	
occurrences (all)	3	1	
Ligament sprain			

subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)
occurrences (all)	2	2
Tibia fracture		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	2	1
Arthropod bite		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Arthropod sting		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Fracture		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Skin abrasion		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Spinal fracture		
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)
occurrences (all)	1	2
Wound		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Animal bite		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Epidural haemorrhage		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Face injury		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Fibula fracture		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Foot fracture		

subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Head injury			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Humerus fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lower limb fracture			
subjects affected / exposed	0 / 132 (0.00%)	3 / 132 (2.27%)	
occurrences (all)	0	3	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Patella fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Procedural headache			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Spinal compression fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Sunburn			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Wrist fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Phimosi			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Talipes			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Tachycardia			
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)	
occurrences (all)	2	2	
Atrioventricular block complete			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Cardiogenic shock			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Cardiomyopathy			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 132 (0.76%)	3 / 132 (2.27%)	
occurrences (all)	1	3	

Myocardial fibrosis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)	
occurrences (all)	1	2	
Sinus tachycardia			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Ventricular hypokinesia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Ventricular tachycardia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Cardiac hypertrophy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Myocardial infarction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pericardial effusion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Pericarditis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Right ventricular hypertrophy			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Systolic dysfunction			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	3	
Nervous system disorders			
Headache			

subjects affected / exposed	32 / 132 (24.24%)	30 / 132 (22.73%)
occurrences (all)	68	168
Dizziness		
subjects affected / exposed	4 / 132 (3.03%)	3 / 132 (2.27%)
occurrences (all)	4	3
Migraine		
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	2	0
Benign intracranial hypertension		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Dystonia		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Periodic limb movement disorder		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Syncope		
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)
occurrences (all)	1	2
Cluster headache		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	2
Coma		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Encephalopathy		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Peripheral sensory neuropathy		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Depression		
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	2	0
Sleep disorder		

subjects affected / exposed occurrences (all)	2 / 132 (1.52%) 2	0 / 132 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)	
occurrences (all)	2	1	
Tympanic membrane perforation			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Eustachian tube dysfunction			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Vertigo positional			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Tympanic membrane hyperaemia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tympanic membrane scarring			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Eye disorders			

Cataract subcapsular subjects affected / exposed occurrences (all)	2 / 132 (1.52%) 2	0 / 132 (0.00%) 0	
Eye pruritus subjects affected / exposed occurrences (all)	2 / 132 (1.52%) 2	0 / 132 (0.00%) 0	
Astigmatism subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	0 / 132 (0.00%) 0	
Cataract subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	0 / 132 (0.00%) 0	
Dacryostenosis acquired subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 3	0 / 132 (0.00%) 0	
Dry eye subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 3	0 / 132 (0.00%) 0	
Eyelid oedema subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	0 / 132 (0.00%) 0	
Myopia subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	0 / 132 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	1 / 132 (0.76%) 1	0 / 132 (0.00%) 0	
Conjunctivitis allergic subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	1 / 132 (0.76%) 1	
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	1 / 132 (0.76%) 1	
Gastrointestinal disorders Vomiting			

subjects affected / exposed	18 / 132 (13.64%)	10 / 132 (7.58%)
occurrences (all)	22	13
Diarrhoea		
subjects affected / exposed	16 / 132 (12.12%)	22 / 132 (16.67%)
occurrences (all)	23	31
Constipation		
subjects affected / exposed	11 / 132 (8.33%)	8 / 132 (6.06%)
occurrences (all)	13	6
Nausea		
subjects affected / exposed	10 / 132 (7.58%)	8 / 132 (6.06%)
occurrences (all)	18	10
Abdominal pain upper		
subjects affected / exposed	9 / 132 (6.82%)	11 / 132 (8.33%)
occurrences (all)	12	14
Abdominal pain		
subjects affected / exposed	8 / 132 (6.06%)	7 / 132 (5.30%)
occurrences (all)	13	10
Dyspepsia		
subjects affected / exposed	3 / 132 (2.27%)	3 / 132 (2.27%)
occurrences (all)	3	4
Abdominal discomfort		
subjects affected / exposed	2 / 132 (1.52%)	3 / 132 (2.27%)
occurrences (all)	2	3
Flatulence		
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	2	0
Gastrooesophageal reflux disease		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	2	1
Toothache		
subjects affected / exposed	2 / 132 (1.52%)	1 / 132 (0.76%)
occurrences (all)	3	1
Abnormal faeces		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Anal pruritus		

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	2	0
Breath odour		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Faeces soft		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Gastritis		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Gastrointestinal disorder		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Gastrointestinal pain		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	2	0
Gingival pain		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Haematochezia		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Oral disorder		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Teething		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Abdominal distension		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Chronic gastritis		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Dysphagia		

subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Faecaloma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Food poisoning			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Hyperchlorhydria			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Lip swelling			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Odynophagia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Catheter site pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	4 / 132 (3.03%)	4 / 132 (3.03%)	
occurrences (all)	4	4	
Dry skin			
subjects affected / exposed	3 / 132 (2.27%)	0 / 132 (0.00%)	
occurrences (all)	3	0	

Eczema		
subjects affected / exposed	3 / 132 (2.27%)	5 / 132 (3.79%)
occurrences (all)	3	4
Dandruff		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Dermatitis allergic		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	2	0
Dermatitis contact		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Ecchymosis		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Erythema		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Mechanical urticaria		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Pigmentation disorder		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Pityriasis rosea		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Psoriasis		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	2	0
Rash		
subjects affected / exposed	1 / 132 (0.76%)	4 / 132 (3.03%)
occurrences (all)	1	4
Rash generalised		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1

Seborrhoea		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Skin ulcer		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Acne		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Alopecia		
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)
occurrences (all)	0	2
Dermatitis bullous		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Dyshidrotic eczema		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Hyperhidrosis		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Ingrowing nail		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	2
Miliaria		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Pruritus		
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)
occurrences (all)	0	2
Rash pruritic		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Skin discolouration		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1

Skin disorder			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Skin lesion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Skin mass			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	11 / 132 (8.33%)	0 / 132 (0.00%)	
occurrences (all)	14	0	
Nephrolithiasis			
subjects affected / exposed	3 / 132 (2.27%)	4 / 132 (3.03%)	
occurrences (all)	4	4	
Choluria			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Glycosuria			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Haematuria			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Haemoglobinuria			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Pollakiuria			

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Ureterolithiasis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Ketonuria			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Urge incontinence			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Urinary hesitation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Endocrine disorders			
Delayed puberty			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Cushingoid			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 132 (6.82%)	15 / 132 (11.36%)	
occurrences (all)	12	25	
Arthralgia			
subjects affected / exposed	7 / 132 (5.30%)	9 / 132 (6.82%)	
occurrences (all)	7	10	
Myalgia			

subjects affected / exposed	5 / 132 (3.79%)	1 / 132 (0.76%)
occurrences (all)	6	1
Scoliosis		
subjects affected / exposed	5 / 132 (3.79%)	1 / 132 (0.76%)
occurrences (all)	6	1
Pain in extremity		
subjects affected / exposed	3 / 132 (2.27%)	3 / 132 (2.27%)
occurrences (all)	3	3
Joint swelling		
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	2	0
Musculoskeletal chest pain		
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)
occurrences (all)	2	2
Osteoporosis		
subjects affected / exposed	2 / 132 (1.52%)	5 / 132 (3.79%)
occurrences (all)	2	5
Bone pain		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Coccydynia		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Dactylitis		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Flank pain		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	2	0
Joint contracture		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	2	2
Joint stiffness		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Muscle hypertrophy		

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)	
occurrences (all)	1	2	
Neck pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Tendon pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Chest wall mass			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Extremity contracture			
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)	
occurrences (all)	0	2	
Foot deformity			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Muscle contracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Delirium			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Nasopharyngitis		
subjects affected / exposed	45 / 132 (34.09%)	36 / 132 (27.27%)
occurrences (all)	68	50
Upper respiratory tract infection		
subjects affected / exposed	18 / 132 (13.64%)	17 / 132 (12.88%)
occurrences (all)	24	24
Gastroenteritis		
subjects affected / exposed	11 / 132 (8.33%)	5 / 132 (3.79%)
occurrences (all)	13	6
Influenza		
subjects affected / exposed	11 / 132 (8.33%)	8 / 132 (6.06%)
occurrences (all)	13	9
Urinary tract infection		
subjects affected / exposed	6 / 132 (4.55%)	2 / 132 (1.52%)
occurrences (all)	6	6
Otitis media		
subjects affected / exposed	5 / 132 (3.79%)	0 / 132 (0.00%)
occurrences (all)	5	0
Pneumonia		
subjects affected / exposed	5 / 132 (3.79%)	0 / 132 (0.00%)
occurrences (all)	6	0
Rhinitis		
subjects affected / exposed	5 / 132 (3.79%)	8 / 132 (6.06%)
occurrences (all)	6	9
Ear infection		
subjects affected / exposed	3 / 132 (2.27%)	8 / 132 (6.06%)
occurrences (all)	3	9
Localised infection		
subjects affected / exposed	3 / 132 (2.27%)	2 / 132 (1.52%)
occurrences (all)	3	2
Lower respiratory tract infection		
subjects affected / exposed	3 / 132 (2.27%)	2 / 132 (1.52%)
occurrences (all)	3	2
Pharyngitis		
subjects affected / exposed	3 / 132 (2.27%)	6 / 132 (4.55%)
occurrences (all)	3	6

Bronchitis		
subjects affected / exposed	2 / 132 (1.52%)	3 / 132 (2.27%)
occurrences (all)	3	5
Dysentery		
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	2	0
Furuncle		
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)
occurrences (all)	2	0
Gastroenteritis viral		
subjects affected / exposed	2 / 132 (1.52%)	3 / 132 (2.27%)
occurrences (all)	2	3
Respiratory tract infection		
subjects affected / exposed	2 / 132 (1.52%)	2 / 132 (1.52%)
occurrences (all)	2	3
Corona virus infection		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Cystitis		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Enterocolitis infectious		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Folliculitis		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Fungal infection		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Fungal skin infection		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Oral fungal infection		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1

Oral herpes		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	3
Paronychia		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Pilonidal cyst		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Rash pustular		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Sepsis		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Sinusitis		
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)
occurrences (all)	1	1
Skin infection		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Tinea versicolour		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Tonsillitis		
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)
occurrences (all)	1	3
Tracheitis		
subjects affected / exposed	1 / 132 (0.76%)	2 / 132 (1.52%)
occurrences (all)	1	3
Viral infection		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0
Wound infection staphylococcal		
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)
occurrences (all)	1	0

Appendicitis perforated		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Body tinea		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Cellulitis		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Conjunctivitis		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Eczema infected		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Gastrointestinal infection		
subjects affected / exposed	0 / 132 (0.00%)	2 / 132 (1.52%)
occurrences (all)	0	2
Genital infection fungal		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Groin infection		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Helicobacter infection		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Herpes zoster		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1
Hordeolum		
subjects affected / exposed	0 / 132 (0.00%)	4 / 132 (3.03%)
occurrences (all)	0	4
Onychomycosis		
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)
occurrences (all)	0	1

Osteomyelitis chronic			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Peritonitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Rhinovirus infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Scarlet fever			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Soft tissue infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Staphylococcal infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Tinea pedis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Wound infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	2	
Fat embolism			
subjects affected / exposed	1 / 132 (0.76%)	1 / 132 (0.76%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 132 (1.52%)	0 / 132 (0.00%)	
occurrences (all)	2	0	
Dehydration			

subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Folate deficiency			
subjects affected / exposed	1 / 132 (0.76%)	0 / 132 (0.00%)	
occurrences (all)	1	0	
Hyperhomocysteinaemia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 132 (0.00%)	1 / 132 (0.76%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2016	<p>Amendment1</p> <ol style="list-style-type: none">1. Amendment to Inclusion criteria to introduce minimum age for study participants: 10 years old at Screening.2. Amendment to Inclusion criteria to allow immunization with any pneumococcal polysaccharide vaccine.3. Amendment to Section 4.4 Pregnancy to update the contraception methods for participating patients and their female partners of childbearing potential as well as the duration of required contraception after last study drug intake.4. Amendment to Section 8.1.5 Assessment of Causality to introduce reference to the IB regarding available safety information with the study drug.5. Introduction of Section 8.2.5 Reporting of the Suspected Unexpected Serious Adverse Reactions (SUSARs) by the Sponsor to provide definition of SUSARs and information about SUSARs reporting.6. Minor editorial changes.
16 August 2016	<p>Amendment 2</p> <ol style="list-style-type: none">1. Amendment to the Synopsis and Section 2.1 Study Objectives to remove the assessment of idebenone pharmacokinetic profile in patients with DMD receiving glucocorticoid steroids2. Amendment to the Synopsis and Section 2.2 Study Endpoints to remove the PK endpoints3. The following Sections were amended to cross-refer to the PK substudy protocol (SIDEROS PK substudy): Synopsis Study Flow Chart 6.1 Outline of Study Procedures 6.2 Schedule of Assessments 6.3 Treatment and Storage of Biological Samples 9.3.2 Efficacy Evaluation4. Amendment to Section 8.2.5 Reporting of the Suspected Unexpected Serious Adverse Reactions (SUSARs) by the Sponsor to also include the process for SUSAR reporting in Switzerland.5. Amendment to Section 8.3.3 Safety Blood Sampling and Urine Analysis to clarify further testing upon an abnormal urinalysis.

08 February 2017	<p>Amendment 3</p> <ol style="list-style-type: none"> 1. Amendment to Synopsis and Section 4.1 Inclusion Criteria to specify that the 15% reproducibility of the FVC repeat refers to relative values. 2. Amendment to Synopsis and Section 4.2 Exclusion Criteria to: <ol style="list-style-type: none"> a. Allow the participation of patients that underwent exon-skipping or read-through gene therapy more than 6 months prior to Screening. b. Clarify the concept of symptomatic heart failure. c. Add a reference to Appendix B for the concept of hepatic impairment, which defines the Child-Pugh Score in chronic liver disease. 3. The following Sections were amended to introduce the collection of demographic data at Screening: Synopsis Study Flow Chart Section 6.1 Outline of Study Procedures Section 6.2 Schedule of Assessments Section 6.2.1 Screening Visit 4. Amendment to Section 8.1.5 Assessment of Causality to update the reference to the Investigator's Brochure regarding the list of AEs. 5. Amendment to Section 9.2.1 Intent-To-Treat Population to remove the word "violations" and replace it by "deviations". 6. Addition of Appendix B to attach the Child-Pugh score in chronic liver disease. 7. Minor editorial changes
04 September 2017	<p>Amendment 4 v 0.9</p> <p>for detailed description of the amendment see Appendix 16.1.1.1 of the CSR</p>
20 November 2017	<p>Amendment 5 v0.1</p> <ol style="list-style-type: none"> 1. The responsible Physician of the study and the corresponding contact details have been changed. 2. Synopsis and Section 4.2 were amended: Exclusion criterion 8 has been changed to reintroduce the exclusion of patients with severe renal impairment (eGFR <30 mL/min/1.73 m²). 3. Minor clarification to Synopsis, Section 4.6 and Section 6.2.13 to specify that withdrawal criteria apply only to randomized patients. 4. The Schedule of Assessments table was corrected to remove "Randomization" mark from Visit 3/Week 13 and Visit 5/Week39. 5. Additional clarification was added to Section 8.1 for the classification of laboratory abnormalities. 6. Addition of a reference in Section 10.
20 June 2018	<p>Amendment 6 (20 June 2018)</p> <p>see Appendix 16.1.1.1 of the CSR</p>
19 May 2020	<p>Addendum 1 (19 May 2020) – Particular measures related to COVID-19 pandemic</p>
22 June 2020	<p>Amendment 7 (22 June 2020)</p> <p>for detailed amendment description see Appendix 16.1.1.1 of CSR</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data from an interim analysis (IA) conducted by an independent DSMB concluded that the study was unlikely to meet its PEP.
Decision to terminate the study was made in October 2020 based on data from the IA. LPLV occurred on 1 Dec 2020.

Notes: